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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,474	11/20/2006	Robert Olivieri	002441.00186	9877

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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
05/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,474	OLIVIERI ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *8 and 16-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on February 17, 2010 is acknowledged. Claims 1-23 are pending. Claims 8 and 16-23 were previously withdrawn. Claim 1 has been amended. Claims 1-7 and 9-15 are currently under examination.

Rejections Withdrawn

2. In view of Applicant's argument, the rejection of claims 1-4, 6 and 9-12 under 35 U.S.C. 102(e) as being anticipated by Lowell et al. (U.S. Patent 6,476,201 B1) is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. The rejection of claims 1-7, 9-12, 14 and 15 under 35 U.S.C. 102(e) as being anticipated by Zollinger et al. (U.S. Patent 6,558,677 B2) is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) Zollinger et al. do not teach “a step of ultrafiltration of crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps."

Applicant’s arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a process for preparing bacterial OMV’s comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

With regard to Point 1, Zollinger et al. disclose a method for the preparation of NOMV. Zollinger et al. disclose that the method comprises shaking flask cultures of *N. meningiditis* strain 9162 grown and harvested as described in example 1. The procedure as described in example 1 was followed up to the first ultracentrifugation step (see column 16, lines 1-9). The Examiner is interpreting this to mean that the procedure stopped at the first ultracentrifugation step and therefore meets the limitation of "prior to any ultracentrifugation or sterilization steps”. Zollinger et al. further disclose that at this point in the process the crude extract was split in two parts. One part of the extract was processed as described below using steps that were *substituted* for the two ultracentrifugation steps used in examples 1 and 2 as a means of purifying the NOMV from the cell extract. The other part of the extract was processed by ultracentrifugation as described in example 1 (see column 16, lines 9-16). The Examiner has interpreted this to mean that of the two parts of crude extract, one part was ultracentrifuged while the second part was not. Moreover, Zollinger et al. disclose that the extract was then processed by ultrafiltration (see column 16, lines 30-33). Lastly, Table 3 discloses that

the NOMV from the crude cell extract contained nucleic acid (see Table 3, Columns 16 and 17).

As previously presented, Zollinger et al. disclose a process for preparing vaccines which comprise outer membrane vesicles from *N. meningitidis.* Zollinger et al. disclose that the vaccine can be prepared by isolating native outer membrane vesicles from the organism or from the culture medium by methods known in the art. Zollinger et al. disclose filtering to sterilizing the solution, diluting the solution, adding an adjuvant and stabilizing the solution (column 9, lines 1-9). Moreover, Zollinger et al. disclose that ultracentrifugation steps can be eliminated by use of the batch-wise adsorption of nucleic acid onto a DEAE ion exchange matrix followed by filtration to remove the ion exchange matrix and then ultrafiltration using a membrane or microfiltration, such as Ultrafiltration cartridge. Zollinger et al. disclose that ultracentrifugation steps were used to separate the OMV (see column 8, lines 43-51). Zollinger et al. disclose the use of centrifugation in a continuous flow sharples centrifuge (see column 14, line 23). Zollinger et al. disclose that the OMV can be added to a pharmaceutically acceptable diluent, carrier or excipient (see column 3, lines 13-16). Zollinger et al. disclose that the present invention include the use of *Neisseria meningitidis* Group B (see column 3, lines 23-25). Zollinger et al. disclose that the outer membrane protein is subject to phase variation in expression wherein mutants with constitutive expression of this protein replace the rmp protein with a copy of the opc gene (see column 6, lines 37-42).

The process of Zollinger et al. is identical to the instantly claimed invention. Absent evidence to the contrary, the ultrafiltration steps necessarily results in diafiltration; is necessarily a cross-flow or tangential flow and necessarily has a cut off of about 300kDa.

4. The rejection of claims 1-7 and 9-13 under 35 U.S.C. 102(e) as being anticipated by Granoff et al. (U.S. 2006/0029621) is maintained for reasons set forth in the previous office action.

Applicant argues that:

1) Paragraph 0085 provides too little detail to determine the order of purification steps that would actually be performed to purify OMVs. Paragraph 0185 goes into detail and utilizes centrifugation followed by ultracentrifugation.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a process for preparing bacterial OMV's comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

With regard to Point 1, paragraph 0085 discloses a process of preparing outer membrane vesicles prepared from the outer membrane of a cultured strain of *Neisseria meningitidis.* Said outer membrane vesicles can be obtained from said strain grown in broth by separating the bacterial cells from the culture medium by filtration or by low speed centrifugation; lysing; and separating an outer membrane fraction by high-speed centrifugation. The claims have been anticipated by Granoff et al. There is no ambiguity in paragraph 0085 because the skilled artisan is either going to separate the cells by filtration or by low speed centrifugation. If the artisan decided to separate the OMV by filtration; lyse and then follow that by separating said OMV by high-speed centrifugation; Granoff et al. has anticipated the claim. There are only two options present, a skilled artisan can only do one of two things. Consequently, paragraph 0085 provides enough detail to determine the order of purification steps performed to purify OMV's.

As previously presented, Granoff et al. disclose a process of preparing outer membrane vesicles prepared from the outer membrane of a cultured strain of *Neisseria*

meningitidis. Said outer membrane vesicles can be obtained from said strain grown in broth by separating the bacterial cells from the culture medium by, for example, filtration or low speed centrifugation, affinity separation or high-speed centrifugation (see paragraph 0085). Granoff et al. disclose the use of adjuvants to enhance the effectiveness of the composition (see paragraph 0091). Moreover, Granoff et al. disclose the use of outer membrane vesicle from Neisseria *meningitidis* serogroup B strain H44/76 (B:15:P1.7,16) (see paragraph 0013).

The process of Granoff et al. is identical to the instantly claimed invention. Absent evidence to the contrary, the ultrafiltration steps necessarily results in diafiltration; is necessarily a cross-flow or tangential flow and necessarily has a cut off of about 300kDa.

5. The rejection of claims 1-7 and 9-15 under 35 U.S.C. 102(e) as being anticipated by Berthet et al. (U.S. 2006/0204520 A1) is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) Paragraph 0036-37 ignores the fact that soluble nucleic acids, proteins and capsular polysaccharides would also need to be removed. Thus, one of skill in the art would perform ultracentrifugation or DEAE chromatography to remove such contaminants.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a process for preparing bacterial OMV's comprising a step of ultrafiltration of a crude OMV preparation containing bacterial DNA prior to any ultracentrifugation or sterilization steps.

With regard to Point 1, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., soluble nucleic acids, proteins and capsular polysaccharide would also need to be removed) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As previously presented, Berthet et al. disclose a process for preparing bacterial OMV's by which vesicles from modified strains are reduced in size by sterile filtration (see paragraph 0058). Preferably, the gram negative bacterium is Neisseria *meningitidis*, which has been genetically modified by down regulating expression of either or both of exbB and exbD genes (see paragraph 0056). Berthet et al. further disclose that one or more genes are preferred for down regulation they include PorA, PorB, PilC, ThpA, TbpB, LbpA, LbpB, Opa, and Opc (see paragraph 0092). Moreover, Berthet et al. disclose the effect of the rmpM mutation on OMV's from H44/76 (see paragraphs 0125-26). Berthet et al. disclose that the blebs may be filter sterilized and that the blebs can be harvested without the use of detergents, which would mean that usual process steps to remove detergent such as chromatography purification and ultra centrifugation may be obviated (see paragraphs 0036-37).

The process of Berthet et al. is identical to the instantly claimed invention. Absent evidence to the contrary, the ultrafiltration steps necessarily results in diafiltration; is necessarily a cross-flow or tangential flow and necessarily has a cut off of about 300kDa.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
5/20/10

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645